The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 24

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JEAN-FRANCOIS BACH and LUCIENNE CHATENOUD

Appeal No. 2000-0989
Application No. 08/986,568

HEARD: November 6, 2001

Before WILLIAM F. SMITH, ROBINSON and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 2, 4-7, 9-13 and 16-18, which are all the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A method of treating spontaneous and ongoing auto-immune diseases in mammals, comprising administering to a mammal, in need of such a treatment, a therapeutically effective amount of one or more non mitogenic anti-CD3 active compounds to achieve permanent disease remission through the induction of antigen-specific unresponsiveness, i.e. immune tolerance.

The references relied upon by the examiner are:

Güssow et al. (Güssow), "Humanization of Monoclonal Antibodies," Methods in Enzymology, Vol. 203, pp. 99-121 (1991)

Chatenoud, et al. (Chatenoud), "Anti-CD3 antibody induces long-term remission of overt autoimmunity in nonobese diabetic mice," Proc. Natl. Acad. Sci. USA, Vol. 91, pp. 123-127 (1994)

Hughes et al. (Hughes), "Induction of T Helper Cell Hyporesponsiveness in an Experimental Model of Autoimmunity by Using Nonmitogenic Anti-CD3 Monoclonal Antibody," J. Immunology, Vol. 153, No. 7, pp. 3319-3325 (1994)

Racadot et al. (Racadot), "Current Concepts in the Treatment of Autoimmune Diseases with Monoclonal Antibodies," Clin. Immunother., Vol. 1, No. 3, pp. 199-208 (1994)

GROUNDS OF REJECTION

Claims 1, 2, 4-5, 9, 13 and 16-18 stand rejected under 35 U.S.C. § 102(b) as anticipated by Chatenoud as evidenced by Hughes.

Claims 1, 2, 4-7, 9-13 and 16-18 stand rejected under 35 U.S.C. § 103 as being unpatentable over Racadot in view of Güssow and Chatenoud.

We affirm the rejection under 35 U.S.C. § 102(b) as a new ground of rejection under 37 CFR § 1.196(b). We reverse the rejection under 35 U.S.C. § 103.

DISCUSSION

In reaching our decision in this appeal, we considered appellants' specification and claims, in addition to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer[1] for the examiner's reasoning in support of the rejections. We further reference appellants' Brief[2], and Reply Brief[3] for the appellants' arguments in favor of patentability. We note the examiner entered and considered the Reply Brief without comment.[4]

THE REJECTION UNDER 35 U.S.C. § 102:

As set forth in Gechter v. Davidson, 116 F.3d 1454, 1457, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997), "[u]nder 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim." "Every element of the claimed invention must be literally present, arranged as in the claim." Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). However, since claim interpretation normally control the remainder of the decisional process, our analysis will begin with the key legal question--what is the invention claimed? Cf. Panduit Corp. v. Dennison Manufacturing Co., 810 F.2d 1561, 1567-68, 1 USPQ2d 1593, 1597 (Fed. Cir. 1987).

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[1] Paper No. 19, mailed January 19, 2000.
[2] Paper No. 18, received November 15, 1999.
[3] Paper No. 20, received March 10, 2000.
[4] Paper No. 21, mailed April 11, 2000.

Claim 1 is drawn to a method of treating spontaneous and ongoing auto-immune diseases in mammals, comprising administering to a mammal, in need of such a treatment, a therapeutically effective amount of one or more non mitogenic anti-CD3 active compounds. According to the specification (page 3), a particularly preferred non mitogenic anti-CD3 active compound is an anti-CD3 antibody $F(ab')_2$ fragment. We note that appellants' specification (page 1) discloses in Chatenoud "the inventors, with other co-authors, have reported that a short term treatment with low doses of an anti-CD3 mAb could restore self tolerance to ß-cell-associated antigens, thus inducing complete and durable remission of the spontaneous auto-immune diabetes, in overtly diabetic NOD [non-obese diabetic] ... mice." Thus, the claimed invention reads on the treatment of spontaneous auto-immune diabetes in a NOD mouse comprising administering to the NOD mouse a therapeutically effective amount of an anti-CD3 antibody $F(ab')_2$ fragment.

According to the examiner (Answer, page 4) Chatenoud "teaches the induction of antigen-specific unresponsiveness in NOD [non-obese diabetic] mice ... by injection of non-mitogenic anti-CD3 monoclonal antibody (mAb) $F(ab')_2$ fragments ... resulting in complete remission of overt disease." The examiner finds (id.) "it is a fact well known in the art that $F(ab')_2$ fragments are non mitogenic because they do not induce the release of cytokines like intact mAbs do, as evidenced by Hughes...."

In response, appellants explain (Brief, bridging paragraph, pages 2-3) that Chatenoud "investigated immuno-intervention of autoimmunity using two non obese diabetic (NOD) mice models. In one model, autoimmune insulin-dependant diabetes mellitus (IDDM) ensues from progressive loss of self-tolerance to β-cell-associated antigens. In a second model, an accelerated model of IDDM is produced by administering cyclophosphamide (CY) to the mice."

According to appellants (Brief, page 3) Chatenoud's "CY-induced diabetes model suggested that short-term, low-dose anti-CD3 treatment is effective for inducing immunosuppression transiently. A determination of the long-term effectiveness of the therapy was precluded because CY treated mice typically die within 50 days of the initial CY administration." In contrast to the CY model, appellants argue (id.), Chatenoud's "spontaneous diabetes model demonstrated that administration of the intact anti-CD3 antibody (but not of the antibody fragments) induces a durable state of antigen-specific unresponsiveness." In view of this contrasting methodology, appellants conclude (Brief, page 5) that:

> the examiner has had to generalize from a similarity of results (transient reduction in insulitis), achieved in one animal model (CY-induced diabetes), to conclude that both therapies also would have been expected to have another effect in common (durable remission of overt autoimmunity), in another model (spontaneous diabetes). Appellants submit, however, that the aforementioned differences between these models would have made this generalization untenable as a matter of fact.

Appellants further argue (Brief, page 5), with reference to the Strom Declaration that "one skilled in the art, at the time of appellants' invention, would not have

expected to obtain a durable, antigen-specific unresponsiveness, upon administration of anti-CD3 antibody fragments."

Upon consideration of the claimed invention, we are unwilling to agree with appellants' analysis. Appellants place a great deal of weight on the words "durable" and "transient", neither of which appears in the claimed invention. Instead the claimed invention provides for a stated end result "to achieve permanent disease remission through the induction of antigen-specific unresponsiveness, i.e.[,] immune tolerance." As we understand appellants' argument (Brief, page 3) Chatenoud's "CY-induced diabetes model suggested that ... anti-CD3 [and anti-CD3 $F(ab')_2$][5] treatment is effective for inducing immunosuppression transiently[, because] ... the long-term effectiveness of the therapy was precluded because CY treated mice typically die within 50 days of the initial CY administration." The claimed method however, is not directed to a new use; it is the same use and it consists of the same steps as described by Chatenoud. We remind appellants that newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent. In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607(CCPA 1978). Stated differently, Chatenoud's method is the same as the claimed method, therefore the result is inherent in the performance of the method.

On reflection, we find no error in the examiner's rejection of claim 1. We note that rather than separately arguing the claims on appeal, appellants have

[5] See Chatenoud, page 126, column 2, first full paragraph.

grouped the claims as standing or falling together. See Brief, page 2. Accordingly, for the purposes of this rejection, claims 2, 4, 5, 9, 13 and 16-18 fall together with claim 1.

However, because our construction of the claimed invention is different from the approach taken in the briefings, we affirm the rejection of claim 1 under 35 U.S.C. § 102(b) as anticipated by Chatenoud, as a new ground of rejection under 35 U.S.C. § 1.196(b). As discussed supra claims 2, 4, 5, 9, 13 and 16-18 fall together with claim 1.

THE REJECTION UNDER 35 U.S.C. § 103:

According to the examiner (Answer, page 5) Racadot "teaches the treatment of multiple sclerosis in human patients with ... a murine monoclonal antibody designated muromonab-CD3...." In addition, the examiner finds (id.) that while Racadot "teaches that the treatment is associated with a dramatic decrease in T cell count and induction of clonal anergy ... [Racadot recognize] a drawback in the treatment in that all patients developed anti-murine Abs and some patients deteriorated during therapy ... and [treatment resulted in] a massive cytokine release...." Notwithstanding these negative teachings in Racadot, the examiner argues (id.) "[t]he skilled artisan would have readily recognized that the massive cytokine release associated with muromonab-CD3 treatment could be averted through the use of $F(ab')_2$ fragments of the mAb as taught by Chatenoud et al." In addition, the examiner relies on Güssow to address Racadot's anti-murine Abs response, finding (id.) that Güssow teach

"that this problem can be overcome by reshaping, humanization, of the murine Ab."

Therefore the examiner concludes (Answer, page 6) that:

> One would have been motivated to combine these references with a reasonable expectation of success by the teachings of Racadot et al[.] and Chatenoud et al[.] that anti-CD3 treatment induces tolerance in an ongoing autoimmune reaction and by the teachings of Chatenoud et al[.] and Güssow et al[.] which address the problems taught to be associated with intact muromonab-CD3 treatment by Racadot et al.

In response, appellants argue (Brief, page 7) that Racadot "did not teach that anti-CD3 therapy is capable of inducing a durable remission of overt autoimmunity." Instead, appellants point out (id.) that Racadot "stated that '[t]he use of muromonab-CD3 in patients with multiple sclerosis appears to be deleterious, with an exacerbation of clinical symptoms in some patients.'" Therefore, appellants conclude (Brief, page 7, and Reply Brief, page 4) "[b]ecause Racadot et al. failed to teach the effectiveness of anti-CD3 therapy, no combination of references would allow one skilled in the art to expect that the success of the present invention could be achieved by modifying the monoclonal antibodies of Racadot...."

The examiner disagrees (Answer, page 8) with appellants' characterization of Racadot as teaching, "treatment with muromonab-CD3 appears to be deleterious in patients...." Instead the examiner finds (Answer, page 9) that Racadot "immediately qualifies this statement with the teaching, "[t]his may [be] due to release of TNF, as TNF is involved in the pathophysiology

of cerebral lesions...." According to the examiner (id.) "Racadot ... goes on to say that ['][t]he use of anti-TNF mAb before infusion of muromonab-CD3 induces a clear down-regulation of this phenomenon and reduces the clinical manifestations of intolerance'." Therefore, the examiner concludes (id.):

> [T]aken in view of the Chatenoud et al[.] reference's teaching regarding success with non-mitogenic anti-CD3 $F(ab')_2$ fragments, one would have had reasonably expected the induction of clonal anergy (nonresponsiveness) seen by Racadot et al[.] ... without the massive detrimental cytokine release associated with intact muromonab-CD3. Further, Racadot et al[.] invites the humanization of murine antibodies ... to alleviate the human-anti-murine-antibody response seen with treatment of human patients with murine antibodies and Güssow et al[.] teaches that full humanization of murine antibodies is even more effective than the chimerization ... suggested by Racadot....

However, in our opinion, the examiner's broad-sweeping characterization of the reference fails to appreciate the specific nuances of each section of the review article. In contrast to the examiner's characterization, Racadot is a review of the "current concepts in the treatment of autoimmune diseases with monoclonal antibodies." See e.g., Title. As set forth in the "Contents" section of the reference, Racadot discuss, inter alia, the targets for monoclonal antibodies, mechanisms of action and clinical results. Therefore, while the same antibodies are discussed in each section, Racadot does not appear to make the same connection between the mechanism of action, "induction of clonal anergy," and the clinical result "deleterious in multiple sclerosis patients, with an exacerbation of clinical symptoms in some patients," as does the examiner. In fact, Racadot refers to different references to support each of these distinct observations.

Compare page 202, second column, first full paragraph, with page 204, first column, first full paragraph.

Upon review of Racadot, we agree with appellants, "Racadot et al. did not teach that anti-CD3 therapy is capable of inducing a durable remission of overt autoimmunity. .... '[t]he use of muromonab-CD3 in patients with multiple sclerosis appears to be deleterious, with an exacerbation of clinical symptoms in some patients.'" See Brief, page 7. Therefore, we agree with appellants' conclusion (id.), "[b]ecause Racadot et al. failed to teach the effectiveness of anti-CD3 therapy, no combination of references [relied on by the examiner] would allow one skilled in the art to expect that the success of the present invention could be achieved by modifying the monoclonal antibodies of Racadot et al."

Therefore, in our opinion, the examiner failed to provide the evidence necessary to support a prima facie case of obviousness. Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Accordingly, we reverse the rejection of claims 1, 2, 4-7, 9-13 and 16-18

under 35 U.S.C. § 103 as being unpatentable over Racadot in view of Güssow and Chatenoud.

REVERSED

WILLIAM F. SMITH)
Administrative Patent Judge)
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DOUGLAS W. ROBINSON) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
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DONALD E. ADAMS)
Administrative Patent Judge)

Appeal No. 2000-09[redacted]
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